IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants   :   James W. Baumgartner et al.

Serial No.   :   09/090,867

Filed   :   June 4, 1998

For   :   TESTIS-SPECIFIC RECEPTOR

                 Examiner   :   Lazar-Wesley, E.

                 Art Unit   :   1646

                 Docket No.:   95-33D1

                 Date   :   July 21, 1999

Assistant Commissioner for Patents

Washington, D.C. 20231

Declaration Under 37 C.F.R. § 1.131

Sir:

We, James W. Baumgartner, Theresa M. Farrah, Donald C. Foster, Frank J. Grant, and Patrick J. O'Hara, do hereby declare as follows:

1. We are the inventors of the above-identified patent application.

2. All of the work described herein was performed in the United States of America by us or under our direction.

3. We have reviewed laboratory notes and other records, including the exhibits submitted herewith, and have determined that the invention recited in claims 1-32 of the above-identified patent application was reduced to practice before March 1, 1996 or was conceived before March 1, 1996 and was subsequently constructively reduced to practice with the filing of the patent application on March 13, 1996.

4. Attached hereto as Exhibit 1 is a copy of a computer printout of the DNA and deduced amino acid sequence of a clone designated "zcytor2." This printout is dated

prior to March 1, 1996. The sequences shown in Exhibit 1 correspond to those disclosed in the patent application in SEQ ID NO:1 and SEQ ID NO:2.

5. Attached hereto as Exhibit 2 is a copy of a portion of a memo written by one of us (Frank J. Grant) before March 1, 1996, which describes particular goals for the WSXWS receptor project, which project included the zcytor2 receptor. As stated in the memo, these goals included preparation of soluble forms (i.e., extracellular ligand-binding domains) of receptors. The memo also describes our intent to clone and express full-length, receptor-encoding cDNAs.

6. Attached hereto as Exhibit 3 is a copy of a page from the notebook of Cameron Brandt, a research associate working under our direction. This page, written before March 1, 1996, describes a plan to prepare polypeptide fusions comprising a soluble receptor and an immunoglubulin Fc polypeptide.

7. Attached hereto as Exhibit 4 is a copy of a slide prepared by one of us (Donald C. Foster) for an in-house seminar on the WSXWS receptor project. This slide was prepared before March 1, 1996. This slide illustrates a plan to express new receptor-encoding DNAs in cultured cells, whereby the cells would produce the encoded receptor.

8. On the basis of these Exhibits we conclude that the invention recited in claims 1-32 of the patent application was reduced to practice before March 1, 1996 or was conceived before March 1, 1996 and was subsequently constructively reduced to practice with the filing of the patent application on March 13, 1996.

We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that the making of willfully false statements and the like is punishable by fine or imprisonment, or both, under

Section 1001 of Title 18 of the United States Code, and may jeopardize the validity of any patent issuing from this patent application.

_____   _____
James W. Baumgartner   Date

Theresa M. Farrah   *19 august 1999*
_____   _____
Theresa M. Farrah   Date

_____   _____
Donald C. Foster   Date

_____   _____
Frank J. Grant   Date

_____   _____
Patrick J. O'Hara   Date

3

HZCYTOR02.SEQ -
Sequence of pcr products generated with 9800-9802,
nested pcr product 9941-AP2 (9801-AP1)
nested pcr product 9937-AP2 (9803-AP1)

Enzyme	Recognition	Cut Site		
Agel	(A^CCGGT)	Def:	1124	
BamHI	(G^GATCC)	Def:	172	
DraI	(TTT^AAA)	Def:	36	
EcoRI	(G^AATTC)	Def:	450	
EcoRV	(GAT^ATC)	Def:	438	
HpaI	(GTT^AAC)	Def:	145	
MscI	(TGG^CCA)	Def:	1244	
MunI	(C^AATTG)	Def:	493	
NcoI	(C^CATGG)	Def:	377	
NsiI	(ATGCA^T)	Def:	592	
Ppu10I	(A^TGCAT)	Def:	588	
SmaI	(CCC^GGG)	Def:	11	
SspI	(AAT^ATT)	Def:	503	988 1107
XmaI	(C^CCGGG)	Def:	9	

HZCYTOR02.SEQ   Linear   LENGTH = 1289

```
           XmaI
             SmaI                    DraI
           | |                       |
   1 CCCCCCGCCCGGGAGAGAGGCAATATCAAGGTTTTAAATCTCGGAGAAATGGCTTTCGTTTGCTTGGCT  69
     GGGGGGCGGGCCCTCTCTCCGTTATAGTTCCAAAATTTAGAGCCTCTTTACCGAAAGCAAACGAACCGA
                                               M   A   F   V   C   L   A
           11                      36
         9
```

```
           HpaI                     BamHI
           |                        |
 139 AAAGTTAACCCTCCTCAGGATTTTGAGATAGTGGATCCCGGATACTTAGGTTATCTCTATTTGCAATGG  207
     TTTCAATTGGGAGGAGTCCTAAAACTCTATCACCTAGGGCCTATGAATCCAATAGAGATAAACGTTACC
     K   V   N   P   P   Q   D   F   E   I   V   D   P   G   Y   L   G   Y   L   Y   L   Q   W
             145                      172
```

```
 208 CAACCCCCACTGTCTCTGGATCATTTTAAGGAATGCACAGTGGAATATGAACTAAAATACCGAAACATT  276
     GTTGGGGGTGACAGAGACCTAGTAAAATTCCTTACGTGTCACCTTATACTTGATTTTATGGCTTTGTAA
     Q   P   P   L   S   L   D   H   F   K   E   C   T   V   E   Y   E   L   K   Y   R   N   I
```

```
 277 GGTAGTGAAACATGGAAGACCATCATTACTAAGAATCTACATTACAAAGATGGGTTTGATCTTAACAAG  345
     CCATCACTTTGTACCTTCTGGTAGTAATGATTCTTAGATGTAATGTTTCTACCCAAACTAGAATTGTTC
     G   S   E   T   W   K   T   I   I   T   K   N   L   H   Y   K   D   G   F   D   L   N   K
```

```
                             NcoI
                             |
 346 GGCATTGAAGCGAAGATACACACGCTTTTACCATGGCAATGCACAAATGGATCAGAAGTTCAAAGTTCC  414
     CCGTAACTTCGCTTCTATGTGTGCGAAAATGGTACCGTTACGTGTTTACCTAGTCTTCAAGTTCAAGG
     G   I   E   A   K   I   H   T   L   L   P   W   Q   C   T   N   G   S   E   V   Q   S   S
                                377
```

```
                       EcoRV        EcoRI
                       |            |
 415 TGGGCAGAAACTACTTATTGGATATCACCACAAGGAATTCCAGAAACTAAAGTTCAGGATATGGATTGC  483
     ACCCGTCTTTGATGAATAACCTATAGTGGTGTTCCTTAAGGTCTTTGATTTCAAGTCCTATACCTAACG
     W   A   E   T   T   Y   W   I   S   P   Q   G   I   P   E   T   K   V   Q   D   M   D   C
                         438          450
```

```
          MunI       SspI
          |          |
 484 GTATATTACAATTGGCAATATTTACTCTGTTCTTGGAAACCTGGCATAGGTGTACTTCTTGATACCAAT  552
     CATATAATGTTAACCGTTATAAATGAGACAAGAACCTTTGGACCGTATCCACATGAAGAACTATGGTTA
     V   Y   Y   N   W   Q   Y   L   L   C   S   W   K   P   G   I   G   V   L   L   D   T   N
            493        503
```

EXHIBIT 1

```
                                    Ppu10I
                                     NsiI
                                     |   |
553 TACAACTTGTTTTACTGGTATGAGGGCTTGGATCATGCATTACAGTGTGTTGATTACATCAAGGCTGAT 621
    ATGTTGAACAAAATGACCATACTCCCGAACCTAGTACGTAATGTCACACAACTAATGTAGTTCCGACTA
    Y  N  L  F  Y  W  Y  E  G  L  D  H  A  L  Q  C  V  D  Y  I  K  A  D
                                          592
                     588


622 GGACAAAATATAGGATGCAGATTTCCCTATTTGGAGGCATCAGACTATAAAGATTTCTATATTTGTGTT 690
    CCTGTTTTATATCCTACGTCTAAAGGGATAAACCTCCGTAGTCTGATATTTCTAAAGATATAAACACAA
    G  Q  N  I  G  C  R  F  P  Y  L  E  A  S  D  Y  K  D  F  Y  I  C  V


691 AATGGATCATCAGAGAACAAGCCTATCAGATCCAGTTATTTCACTTTTCAGCTTCAAAATATAGTTAAA 759
    TTACCTAGTAGTCTCTTGTTCGGATAGTCTAGGTCAATAAAGTGAAAAGTCGAAGTTTTATATCAATTT
    N  G  S  S  E  N  K  P  I  R  S  S  Y  F  T  F  Q  L  Q  N  I  V  K


760 CCTTTGCCGCCAGTCTATCTTACTTTTACTCGGGAGAGTTCATGTGAAATTAAGCTGAAATGGAGCATA 828
    GGAAACGGCGGTCAGATAGAATGAAAATGAGCCCTCTCAAGTACACTTTAATTCGACTTTACCTCGTAT
    P  L  P  P  V  Y  L  T  F  T  R  E  S  S  C  E  I  K  L  K  W  S  I


829 CCTTTGGGACCTATTCCAGCAAGGTGTTTTGATTATGAAATTGAGATCAGAGAAGATGATACTACCTTG 897
    GGAAACCCTGGATAAGGTCGTTCCACAAAACTAATACTTTAACTCTAGTCTCTTCTACTATGATGGAAC
    P  L  G  P  I  P  A  R  C  F  D  Y  E  I  E  I  R  E  D  D  T  T  L


898 GTGACTGCTACAGTTGAAAATGAAACATACACCTTGAAAACAACAAATGAAACCCGACAATTATGCTTT 966
    CACTGACGATGTCAACTTTTACTTTGTATGTGGAACTTTTGTTGTTTACTTTGGGCTGTTAATACGAAA
    V  T  A  T  V  E  N  E  T  Y  T  L  K  T  T  N  E  T  R  Q  L  C  F


                          SspI
                          |
967 GTAGTAAGAAGCAAAGTGAATATTTATTGCTCAGATGACGGAATTTGGAGTGAGTGGAGTGATAAACAA 1035
    CATCATTCTTCGTTTCACTTATAAATAACGAGTCTACTGCCTTAAACCTCACTCACCTCACTATTTGTT
    V  V  R  S  K  V  N  I  Y  C  S  D  D  G  I  W  S  E  W  S  D  K  Q
                          988


1036 TGCTGGGAAGGTGAAGACCTATCGAAGAAAACTTTGCTACGTTTCTGGCTACCATTTGGTTTCATCTTA 1104
     ACGACCCTTCCACTTCTGGATAGCTTCTTTTGAAACGATGCAAAGACCGATGGTAAACCAAAGTAGAAT
     C  W  E  G  E  D  L  S  K  K  T  L  L  R  F  W  L  P  F  G  F  I  L


     SspI                 AgeI
     |                    |
1105 ATATTAGTTATATTTGTAACCGGTCTGCTTTTGCGTAAGCCAAACACCTACCCAAAAATGATTCCAGAA 1173
     TATAATCAATATAAACATTGGCCAGACGAAAACGCATTCGGTTTGTGGATGGGTTTTTACTAAGGTCTT
     I  L  V  I  F  V  T  G  L  L  L  R  K  P  N  T  Y  P  K  M  I  P  E
     1107                 1124


1174 TTTTTCTGTGATACACATGAAGACTTTCCATATCAAGAGACATGGTATTGACTCAACAGTTTCCAGTCATG 1242
     AAAAAGACACTATGTACTTCTGAAAGGTATAGTTCTCTGTACCATAACTGAGTTGTCAAAGGTCAGTAC
     F  F  C  D  T  .


     MscI
     |
1243 GCCAAATGTTCAATATGAGTCTCAATAAACTGAATTTTTCTTGCGAA 1289
     CGGTTTACAAGTTATACTCAGAGTTATTTGACTTAAAAAGAACGCTT

     1244
```
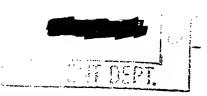
DRAFT

███████

Outline of things to consider for patent application of novel type I cytokine receptors

We have identified partial cDNA sequences for three new members of the type I cytokine receptor family. These receptors are characterized by a conserved cysteine pattern and an amino acid motif containing WSXWS. Members of this family include the receptors for TPO, EPO, Growth Hormone, Prolactin, IL-4, IL-7, IL-9, IL-2, IL-5, IL-3, GM-CSF, IL-6, CNTF, G-CSF and Leukemia inhibitory factor.

The main utility for these sequences would be to facilitate the cloning of the unknown ligands for the receptors. The receptors themselves (ie. soluble forms) might be potential therapeutics as well.

There are at least three ways the receptor sequence can be utilized to clone the ligands:
        a). Make receptor dependent cell lines (as was done in the ███ project) for use in an expression cloning project.
        b). Soluble forms of the receptor can be labeled and used as probes in an expression cloning system.
        c). The receptor could be attached to various columns or other supports and used to purify the ligand.
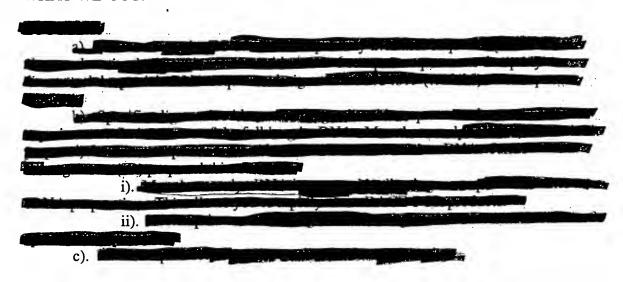
Patentable entities: (???????)
        a). The EST (expressed sequence tag) that allowed us to identify the partial sequence as novel member of the family.
                i). Allows us to clone the full length cDNA.
        b). The full length receptor encoding cDNA.
        c). Homologues of the cDNAs. It may be that murine versions of these receptors are necessary for ligand dependent cell line cloning.
        d). The ligands for the receptors.
        e). AIDS therapies. — *Disc.. w/ Frank*

WHAT WE GOT:

███████
        a) ██
        ██
        ██
        ███
        ██
        ██
        ████████████████████████████████████
                i). ██
        ██
                ii). ██████████████████████████████████
        c). ██

EXHIBIT 2

CONSTRUCTION PLAN IgG γ_1 VECTOR

PURPOSE: WILL BUILD A VECTOR FOR EXPRESSION OF SOLUBLE RECEPTORS FUSED TO IgG γ_1 HEAVY CHAIN. THIS EXPRESSION SYSTEM ALLOWS AN EASY WAY TO PURIFY SOLUBLE RECEPTOR OVER A PROTEIN A COLUMN & THEN PROVIDES A HANDLE FOR USING IN GOING AFTER LIGAND.

F_c PORTION OF IgG γ_1

- IgG PORTION OF FUSION INCLUDES HINGE REGIONS CH_2 & CH_3
- FUSION IS CONSTRUCTED AS A MONOMER BUT DIMERIZES VIA IT'S TWO CYSTEINE'S IN THE HINGE REGION

PLAN

5':

                ARG   SER.

GLU - PRO - LYS - SER - CYS - ASP - LYS - THR - HIS - THR ...

└ 1st A. ACID OF HINGE REGION

    └ LYS CHANGED TO ARGININE TO ALLOW CONSTRUCTION OF Bgl II SITE (FAWSLOW, ET AL. J. OF IMMUNOLOGY 149:655-660

                └ CYS CHANGED TO SER JULY 15, 1992. TO ELIMINATE UNBOUND CYS IN HINGE REGION. THIS CYS NORMALLY BINDS LIGHT CHAIN, BUT LIGHT CHAIN IS NOT NECESSARY FOR CREATION OF A FUNCTIONAL FUSION (BENNETT, ET AL. J. OF BIOL. CHEMISTRY 266 (34) 23060-23067 DEC 5, 1991)

3':   WILL BE IDENTICAL TO HAN ...
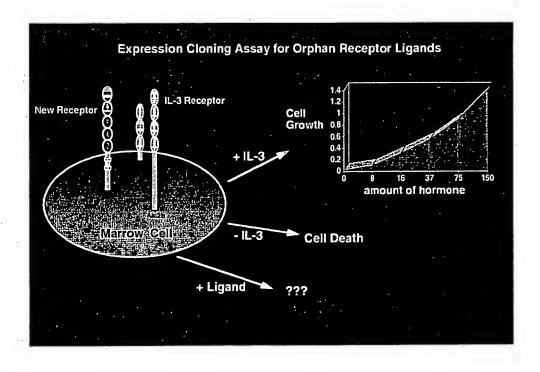
EXHIBIT 3

Expression Cloning Assay for Orphan Receptor Ligands

EXHIBIT 4